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(57) Abstract

This invention refers to injectable aqueous formulations containing radiopaque contrast agents useful for X-ray imaging of human or animal body. This invention specially deals with injectable aqueous solutions of mixtures of non-ionic and water-soluble iodinated aromatic compounds preferably constituted by: a) compounds comprising an aromatic nucleus at least triiodo-substituted; b) compounds comprising at least two aromatic nuclei variably bound together, each one at least triiodo substituted.

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AQUEOUS INJECTABLE FORMULATIONS USEFUL FOR RADIO-DIAGNOSIS COMPRISING IODINATED AROMATIC COMPOUNDS USED AS X-RAY CONTRAST MEDIA

This invention refers to injectable aqueous formulations containing radiopaque contrast agents useful for X-ray imaging of human or animal body.

One of the preferred aspects of this invention specially deals with injectable aqueous solutions of mixtures of non-ionic and water-soluble iodinated aromatic compounds preferably constituted by:

a) compounds comprising an aromatic nucleus at least triiodo-substituted - from now on referred to as monomers or monomeric,

b) compounds comprising at least two aromatic nuclei variably bound together, each one at least triiodo substituted - from now on referred to as dimers or dimeric.

Beyond the compounds of type a) and b), this invention also includes other possible mixtures comprising opacifying derivatives with molecular structures of three or more polyiodinated aromatic nuclei.

Formulations containing X-ray contrast agents (CM) have long been used to enhance the image contrast of human and animal cavities in X-ray examinations. Among the past radiopaque products which have been investigated, it is worth mentioning derivatives of elements such as Ba, Bi, Ta. But afterwards it was found that certain classes of water-soluble brominated and/or iodinated organic compounds are far greatly

useful as contrast agents for the vascular system.

2,4,6-triiodo-benzene derivatives are commonly used as iodinated aromatic X-ray-opaque compounds since their remaining positions 1,3,5 are substituted by suitable organic substituents to reach a sufficient watersolubility, a iodine concentration of 300-450 g/L or more, and a good tolerability.

A good solubility, for example, can be obtained through the introduction on the aromatic nucleus of carboxylic functions which can be salified. These compounds are the so-called ionic iodinated contrast agents. A typical example is the diatrizoic acid (3,5-diacetamido-2,4,6-triiodobenzoic acid) and its meglumine salt, particularly used in angiography. It is highly water-soluble and has a relatively low molecular weight. These features allow injectable solutions with a high iodine content and a low viscosity, essential for a good vascular X-ray imaging.

Unfortunately, ionic contrast media solutions show a high toxicity. Furthermore they are hyperosmotic to plasma (the presence of ions considerably increases osmolality and therefore the osmotic pressure when compared to other physiological fluids), causing possible painful effects in patients after injection. Other drawbacks related to ionic contrast agents rely on the presence of massive counter-cation concentrations (Na^+, $Ca2^+$ and others): the consequence is an increase in the osmotic load, that's to say the amount of administered osmoles, pro dose. It is known that a high osmotic load causes a toxicity increase. Moreover cardiovascular effects may occur as a result

of the increase in plasma volume.

To overcome this problem, non-ionic iodinated agents have been developed, where the substituents on the aromatic nucleus have no ionizable functions. In this case a sufficient water-solubility is granted by highly hydrophilic neutral groups in positions 1,3,5 of the aromatic nucleus. Non-limiting examples of compounds belonging to this last mentioned class of opacifying agents are given by "iopamidol" (BRACCO), or N,N'-bis-[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5-lactamido-isophthalamide, and "iomeprol" (BRACCO) or N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(N-methyl-hydroxyacetylamino)-isophthalamide.

Disregarding the improvements obtained on non-ionic aromatic triiodo-derivatives, there was still the need of decreasing the osmolality in the corresponding opacifying injectable formulations in order to obtain an osmotic pressure more similar to blood. Osmolality is the common term used to relate molality to osmotic pressure. In fact, highly concentrated solutions of different iododerivatives, can show osmolality values that are too high to be tolerable by the human body. By way of an example, a 1 osmol/kg H_2O (=1000 mosmol/kg) solution can generate a 25.5-atm or 2.58-MPa osmotic pressure, hence a physiologically unacceptable value. A way to decrease osmolality, by keeping the total iodine content of aqueous solutions between a desired range, is favouring molecular aggregation. Another way consists in increasing the number of atoms of iodine per molecule, for instance by covalently binding together two or more triiodinated aromatic nuclei

through suitable alkylenic bridges, functionally substituted or not, to obtain the so-called oligomeric or dimeric structures. However in this case, the viscosity of said compounds usually reaches values scoring more than 8-14 mPa7s. This range is generally considered the highest acceptable limit for catheter administrations of opacifying solutions at a rate compatible with the vascular system imaging.

Referring to the above mentioned problems, a wide bibliographic documentation is available comprising technical articles, patents and books. Quite useful documents can be: "X-Ray Contrast Media", by U. Speck published by Medical Division, Department of Medical Information, Schering AG (DE); D.P. Swanson et al., "Pharmaceuticals in Medical Imaging" (1990) Mc Millan Publ. Co.; "Radiocontrast Agents", by M. Sovak, published by Springer Verlag (1984), M. Elke et al., "Kontrastmittel in der radiologischen Diagnostik", G. Thieme Verlag Stuttgart, New York (1992).

Table 1 reports data, disclosed in the prior art, of some well-known iodinated contrast agents, considering the corresponding osmolality and viscosity values of their aqueous solutions according to certain iodine concentrations. Letters i, ni, m, d, stand for compound structural characteristics (i - ionic; ni - non ionic; m - monomer; d - dimer).

Table 1

Compound or medium solution	Structure		Iodine (g/L)	Osmolality H_2O mosmol/kg	Viscosity at 37°C (mPa·s)
Blood	-		-	290	4
diatrizoate (meglumine)	i	m	282	1500	4
ioxaglate	i	d	320	580	7.5
iopromide	ni	m	300	630	4.6
iopamidol	ni	m	300	620	4.5
iomeprol	ni	m	300	521	4.5
iohexol	ni	m	300	690	6.1
metrizamide	ni	m	300	485	6.2
ioversol	ni	m	320	702	5.8
iogulamide	ni	m	300	1040	9.6
iodixanol	ni	d	300	200	8.7
iodecol	ni	d	300	320	7.2
iotrol	ni	d	300	320	8.1
iofratol	ni	d	300	141	8.5
EP-23992 B (compound A, Ex. 15)	ni	d	300	184	7.4

The data of Table 1 show that, osmolality levels are still too high if compared to blood (about 300 mosmol/kg), despite the shift from ionic to non-ionic contrastographic compounds which remarkably reduces the injectable solution osmolality if a iodine concentration of about 300 g/L is used. A way to further reduce osmolality, down to the blood value or even lower values, is using iodinated compounds such as dimers. But, on the other hand, viscosity is too high for most of diagnostic applications requiring quick injections of opacifying formulations into the vascular system. It is worth remembering that in the X-ray vascular imaging, iodine delivery rate is very important. The rate is expressed in grams of iodine per second at 370C [g(iodine)/s], meanwhile the injection pressure through less invasive catheters (i.e. Cordis.4F) is of about 61.2 atm or 6.20 MPa. Obviously, iodine delivery rate depends on the solution concentration and on the volumetric flow rate, which is connected to viscosity and the kind of flow.

Furthermore, in some cases, dimeric solutions are hypotonic and this requires a salt addition to their formulations to reach the isotonicity with blood.

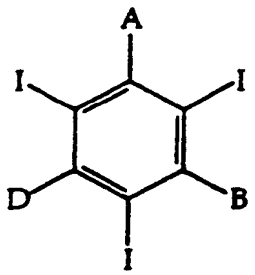
Patent application GB-A-2050167 (Mallinckrodt) claims that it is possible obtaining X-ray opacifying compositions that, at a iodine concentration of 34-40% in weight, have a viscosity lower than 9-10 mPa*s at 370°C, when solutions containing mixtures of ionic and non-ionic iodinated contrast agents are prepared. But as a matter of fact, this approach does not overcome the above mentioned difficulties since the

neutralisation of counter-cations is still necessary. The results is an increase in osmolality and the osmotic load, despite the acceptable viscosity values possibly obtained.

Other documents which can be cited as a reference to the state of the art are: US 3701771, US 4396598, US 5019271, WO 92/09562, WO 92/13636, WO 89/08101, EP 390242, EP 437444, EP 306364. Nevertheless none of them gives a satisfactory answer to the above disclosed problems.

This invention provides important and significant advantages in the field of injectable formulations of iodinated contrast media for X-ray imaging. It was unexpectedly and surprisingly found that injectable aqueous compositions, comprising mixtures of non-ionic iodinated aromatic compounds monomer of type (a) and dimers of type (b), not only have an intermediate osmolality compared to the pure solutions of (a) and (b), and are also isoosmolal or isotonic to the plasma but they also have a lower viscosity than the expected, and a lower toxicity than those shown by the corresponding pure solutions of (a) and (b). Furthermore, during the injection, they supply a favourable iodine delivery rate through less invasive catheters.

Compounds (a) preferably have a structure as indicated in the following general formula (I)



(I)

wherein:

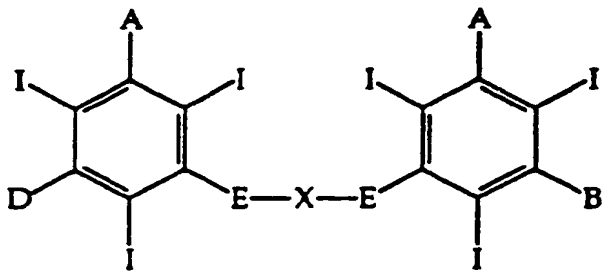
A, B, D, which are the same or different, are $-CON(R)R_1$ or $-N(R)-CO-R_2$ groups, wherein

R is H or a linear or branched alkyl residue (C_1-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups,

R_1 is a linear or branched alkyl residue (C_2-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups, or by one of the two groups $-NH-CO-R_1$ or $-CO-N(R)R_1$, or R_1 is the residue of a carbohydrate, or R_1 and R, taken together, are an alkylene chain (C_3-C_7) which can be interrupted by O, S, N,

R_2 is a linear or branched alkyl residue (C_1-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups, and can also include an oxo group.

Compounds (b) preferably have the following formula (II)



(II)

wherein:

A, B, D, which are the same or different, have the same meanings of formula I,

E, which are the same or different, are selected among -CO-N(R)-, -N(R)-CO-, -N(COR_3)- groups where R has the same meanings of formula (I) and R_3 is an alkyl residue (C_1-C_3) optionally substituted by 1-2 OH or by alkoxy or hydroxyalkoxy groups,

X is a covalent bond or a linear or branched alkylene chain (C_1-C_8), which can be substituted by 1-6 OH groups and/or -CO-NHR groups, and which can be interrupted by -O-, -S-, -N-, -N(R)-CO groups, being R as above defined in formula (I).

Among monomers of type (a), particularly preferred are those listed in Table 2.

Table 2 - Preferred compound of type (a)

Generic Name (source) CAS [RN]	FORMULA I A	B	D
metrizamide [31112-62-6]	-CONHCH(CHOH)$_3$CH$_2$OH CHO	-N(Me)Ac	-NH-Ac
iopamidol [60166-93-0]	-CONHCH(CH$_2$OH)$_2$	-CONHCH(CH$_2$OH)$_2$	-NHCOCH(OH)CH$_3$
iomeprol [78649-41-9]	-CONCH$_2$CH(OH)CH$_2$OH	-CONCH$_2$CH(OH)CH$_2$OH	-N(Me)COCH$_2$OH
iopromide [73334-07-3]	-CONCH$_2$CH(OH)CH$_2$OH	-CONCH$_2$CH(OH)CH$_2$OH Me	-NHCOCH$_2$OMe
ioversol [877771-40-2]	-CONCH$_2$CH(OH)CH$_2$OH	-CONCH$_2$CH(OH)CH$_2$OH	-N-COCH$_2$OH CH$_2$CH$_2$OH
iohexol [66108-95-0]	-CONCH$_2$CH(OH)CH$_2$OH	-CONCH$_2$CH(OH)CH$_2$OH	-N-Ac CH$_2$CH(OH)CH$_2$OH
iopentol [89797-00-2]	-CONCH$_2$CH(OH)CH$_2$OH	-CONCH$_2$CH(OH)CH$_2$OH	-N-Ac CH$_2$CH(OH)CH$_2$OMe

Table 2 (continued)

Generic Name (source) CAS [RN]	FORMULA I A	B	D
ioxilan [107793-72-6]	$-CONCH_2CH_2OH$	$-CONCH_2CH(OH)CH_2OH$	$-N(CH_2CH(OH)CH_2OH)-Ac$
II-1 [99139-49-8]	$-CONCH_2CH(OH)CH_2OH$	$-N(CH_2CH(OH)CH_2OH)-Ac$	$-N(CH_2CH(OH)CH_2OH)-Ac$
iogulamide [75751-89-2]	$-CONHCH_2CH(OH)CH_2OH$	$-CONCH_2CH(OH)CH_2OH$	$-NHCOCO(CHOH)_3CH_2OH$
ioglucol [63941-73-1]	-CONHMe	$-NHCOCH(OH)_4CH_2OH$	$-N(CH_2CH_2OH)-Ac$
ioglucamide [63941-74-2]	-CONHMe	$-NHCOCH(OH)_4CH_2OH$	$-NHCOCHOH)_4CH_2OH$
ioglunide [56562-79-9]	$-CONHCH_2CH_2OH$	$-NHCOCH(OH)_4CH_2OH$	-N(Me)Ac
MP-7011 [76984-84-0]	$-CONHCH_2(CHOH)_5CH_2OH$	-N(Me)Ac	-NH-Ac
MP-7012 [64965-50-0]	$-CONHCH_2CONH(CH_2OH)CH(CHOH)_3CH_2OH$	-N(Me)Ac	-NH-Ac

Table 2 (continued 2)

Generic Name (source) CAS [RN]	FORMULA I A	B	D
MP-10007 [77111-65-0]	$-CONHCH_2CH_2OH$	$-NHCOCO(CHOH)_3CH_2OH$	$-NHCOCO(CHOH)_3CH_2OH$
VA-7-88 [79944-49-3]	$-CONHCH(CH_2OH)CH_2OH$	$-CONHCH(CH_2OH)CH_2OH$	$-N(Me)Ac$
(EP 033426) [79944-51-7]	$-CONHCH(CH_2OH)CH_2OH$	$-CONHCH(CH_2OH)CH_2OH$	$-CONHCH(CH_2OH)CH_2OH$
iosimide [79211-10-2]	$-CON(CH_2CH_2OH)_2$	$-CON(CH_2CH_2OH)_2$	$-CON(CH_2CH_2OH)_2$
iocibidol [79211-34-0]	$-CONCH_2CH(OH)CH_2OH$ (Me)	$-CONHCH_2CHCH_2OH$ (OH)	$-CONH_2$
(EP 0177414) [103876-29-5]	$-N(Ac)CH_2CH(OH)CH_2OH$	$-N(Ac)CH_2CH(OH)CH_2OH$	$-N(Ac)CH_2CH(OH)CH_2OH$

Among dimeric compounds of type (b), particularly preferred are those listed in Table 3.

Table 3 - Preferred compounds of type (b)

Generic Name (source) CAS [RN]	FORMULA II		
	A	B=D	E-X-E
iofratol [141660-63-1]	$-CONHCH(CH_2OH)_2$	$-NHCOCH(OH)CH_3$	$-CONHCH_2\underset{\underset{OH}{|}}{CH}CH_2OH$
iodixanol [92339-11-2]	$-CONHCH_2CH(OH)CH_2OH$	$-CONHCH_2CH(OH)CH_2OH$	$-N\underset{\underset{Ac}{|}}{CH_2}\underset{\underset{OH}{|}}{CH}\underset{\underset{Ac}{|}}{CH_2}N-$
iotrol [79770-24-4]	$-CONH\underset{\underset{CH_2OH}{|}}{CH}CH(OH)CH_2OH$	$-CONH\underset{\underset{CH_2OH}{|}}{CH}CH(OH)CH_2OH$	$-N\underset{\underset{Me}{|}}{COCH_2CO}N-\underset{\underset{Me}{|}}{}$
iotasul [71767-13-0]	$-CON\underset{\underset{Me}{|}}{CH_2}CH(OH)CH_2OH$	$-CON\underset{\underset{Me}{|}}{CH_2}CH(OH)CH_2OH$	$-NHCOCH_2CH_2\diagdown\!\!\diagup S\diagup\!\!\diagdown CH_2CH_2NHCO-$
iodecol [81045-33-2]	$-CONHCH(CH_2OH)_2$	$-CONHCH(CH_2OH)_2$	$-N\underset{\underset{CH_2CH_2OH}{|}}{}-COCH_2CO-N\underset{\underset{CH_2CH_2OH}{|}}{}-$
(WO 92/08691) [143200-04-8]	$-CONHCH_2CH(OH)CH_2OH$	$-NHCOCH_2OH$	$-CONHCH_2\underset{\underset{OH}{|}}{CH}CH_2NHCO-$
(WO 92/08691) [143199-77-3]	$-CONHCH(CH_2OH)_2$	$-NHCOCH_2OH$	$-CONHCH_2\underset{\underset{OH}{|}}{CH}CH_2NHCO-$

Table 3 (continued)

Generic Name (source) CAS [RN]	FORMULA II A	B-D	E-X-E
(WO 92/08691) [143200-00-4]	-CONHCH$_2$CH(OH)CH$_2$OH	-NHCOCH$_2$OH	-CONHCH$_2$C(CH$_2$OH)(CH$_2$OH)CH$_2$NHCO-
(US 4348377) [78341-84-1]	-CONHCH$_2$CH(OH)CH$_2$OH (B 17500)	-CONHCH$_2$CH(OH)CH$_2$OH	-NCH$_2$CH$_2$CH$_2$N- (COCH$_2$OH, COCH$_2$OH)
(EP 0308364) [122731-47-9]	-CONCH$_2$CH(OH)CH$_2$OH (Me)	-CONHCH$_2$CH(OH)CH$_2$OH	-NCOCH$_2$CON- (Me, Me)
(EP 0308364) [122731-49-1]	-CONHCHCH(OH)CH$_2$OH (CH$_2$OH)	-CONHCH$_2$CH(OH)CH$_2$OH	-NCOCH$_2$CON- (Me, Me)
(WO 85/01727) [99139-65-8]	-NCH$_2$CH(OH)CH$_2$OH (Ac)	-NCH$_2$CH(OH)CH$_2$OH (Ac)	-CONHCH$_2$CH$_2$NHCO-
(WO 85/01727) [99139-62-5]	-NCH$_2$CH(OH)CH$_2$OH (Ac)	-NCH$_2$CH(OH)CH$_2$OH (Ac)	-CON-CH$_2$CH$_2$NHCO- (CH$_2$CH$_2$OH)
(EP 0023992) [78341-84-1]	-CONHCH$_2$CH(OH)CH$_2$OH	-CONHCH$_2$CH(OH)CH$_2$OH	-NCH$_2$CH$_2$CH$_2$N- (COCH$_2$OH, COCH$_2$OH)

Particularly preferred contrastographic compositions of this invention comprise the following iodinated monomer and dimer mixtures: iopamidol/iofratol; iomeprol/iofratol; iomeprol/compound A [EP 23992 B: Ex.15]; iopamidol/compound A; iohexol/iodixanol; iopromide/iodecol; iopromide/iotrol; iomeprol/iodecol; iomeprol/iodixanol; iopentol/iodixanol and all their combinations.

In the compositions of this invention the respective proportions of compounds (a) and (b) can limitlessly vary within the range indicated in the claims (i.e. (a) and (b) are present in the mixture in such a ratio that the iodine quantity of (b) can range between 10-90% in weight, preferably between 20-75%, of the total iodine content in the composition, while the chosen values basically depend upon the specific diagnostic use and the desired properties of the injectable preparation. Some of them can be mentioned: iodine concentration, osmolality, viscosity, distribution flow in circulation or in other cavities, time of retention in the organs to be examined, excretion and ways of elimination. Specific data concerning the above mentioned parameters are reported in the following experimental examples.

The formulations of this invention, which mixture of opacifying agents (a) and (b) is totally dissolved to give iodine concentrations of 200-450 g/L or more, are particularly suitable for the angiographic imaging of small vessels, i.e. in brain and cerebrospinal cavities, requiring a low viscosity contrast liquid injection.

According to the use, viscosity can be kept between 4-12 mPa*s, while osmolality can vary between 250-500 mosmol/kg. It was particularly surprising that the mixtures of compounds (a) and (b) according to the present invention showed a better tolerability - especially neurotropic - than the one expected by adding those of the single components. The reason for this unexpected remarkable advantage has no explanation yet.

The performance of the compositions of this invention is completed and increased by the addition of a series of additives, particularly stabilisers, agents controlling the dissolution, buffers (i.e. TRIS) or also biologically acceptable mineral salts.

The additives of the formulations of this inventions are those commonly known and used in the pharmaceutical technique.

As matter of non-limiting example, the following salts and compounds can be cited as particularly preferred additives: halides, carbonates, bicarbonates, sulphates, Na^+, Mg^{2+}, Ca^{2+}, phosphates, tromethamol, EDTA, EDTA $CaNa_2$, heparin, hirudin, glycerol, polyethyleneglycol, dextran and the like.

During the preparation of the composition of this invention, the various ingredients are preferably gradually diluted into a suitable aqueous medium. One of the preferred procedure, for example, can be summed up as follows:

one or more iodinated compounds - monomers and dimers - are dissolved in distilled water in successive portions, with the possible addition of additives. The

resulting solution is submitted to ultrafiltration by using a porously calibrated membrane, as described in the following examples. Then sterilisation is performed according to the standard methods used to prepare X-ray injectable contrast medium formulations.

Other aspects of this invention are more extensively described in the following section.

EXAMPLE 1

An injectable contrastographic composition has been prepared by adding into water the following ingredients: 246.3 g of iomeprol (0.324 mol), 342.2 g of iofratol (0.234 mol), 0.8 g of tromethamol, 0.36 g of concentrated HCl. The resulting solution has been firstly taken to 1 L and then depyrogenated through ultrafiltration by using a cellulose membrane Amicon^R Y10 (10000 Dalton) [temperature = 45±5°C; loading pressure = 5 kg/cm^2; permeate flow rate = 55 mL/s]. Then, sterilisation is carried out for 30 min at 120°C. The resulting solution, containing 300 g of iodine per L, has been labelled as "iomeprol/iofratol 300". In a similar way another solution, labelled as "iomeprol/iofratol 320", has been prepared using 255.6 g of iomeprol (0.366 mol), 373.8 g of iofratol (0.256 mol), 0.79 g of tromethamol and 0.38 of concentrated HCl (iodine content = 320 g/L).

In addition, two 1 L control solutions have been prepared. They contained 0.8 g of tromethamol and 0.36 mg of HCl in addition to the following contrastographic agents:

1° labelled as : "iofratol 300", containing 576.1 g/L of iofratol

2° labelled as : "iomeprol 350", containing 714.4 g/L of iomeprol.

The intracerebral toxicity of the previous solution has been determined by using mice of both sexes, carrying out the experimental protocol described in J.T. Litchfield et al., Pharmacol. Exp. Ther. 96 (1949), 99.

LD_{50} values, expressed in g (iodine)/kg, were the following:

iomeprol/iofratol 300	> 1.5
iomeprol/iofratol 320	> 1.6
iomeprol 350	= 1.30 (1.18-1.44)
iofratol 300	= 0.65 (0.57-0.73)

As clearly shown by the previous data, LD_{50} values in iomeprol/iofratol mixtures were surprisingly higher than those foreseable from the two control solutions. Unfortunately, the exact values were not determined, since higher volumes could not be technically administered to animals.

EXAMPLE 2

A solution of iomeprol/iofratol 300 (1L) is prepared according to the procedure described in Example 1.

Said solution has a newtonian hydrodynamic behaviour, a viscosity value (measured at 37°C) of 6.24 mPa·s and osmolality of about 300 mosmol/kg (osmometric method of vapour pressure).

The iodine delivery rate Q (expressed in g of iodine/s) is measured by means of a 6 hole, 90-cm pigtail Cordis^R 4F catheter at a temperature of 37°C and at a pressure of about 58.5 atm or 5.92 mPa. In the

same way, Q values are measured in control solutions of iomeprol 300 and iofratol 300. The resulting values are reported in the following table:

Solution	Q g (iodine)/s	Osmolality (mosmol/kg)
iomeprol/ iofratol 300	3.79	300
iomeprol 300	4.13	517
iofratol 300	3.43	141

When compared to pure compound solutions, the advantages of the mixture are striking: osmolality is practically equivalent to blood, while the catheter flow rate is higher than the pure dimeric and a bit lower than the pure monomeric, which is greatly hyperosmolal.

EXAMPLE 3

A solution (1L) containing a mixture of 178.12 g of iomeprol (0.234 mol) and 596.35 g of iofratol (0.408 mol) is prepared according to the procedure described in Example 1.

The resulting solution (labelled as "iomeprol/iofratol 400") has a iodine content of 400 g (iodine)/L.

The two control solutions are prepared according to the procedure of Example 1:

"iomeprol 400": 798.95 g of iomeprol in 1L of solution (400 g (iodine)/L)

"iofratol 400": 767.45 g of iofratol in 1L of

solution (400 g (iodine)/L).

The viscosity of the three solutions is measured at 37°C by means of a Haake CV100 viscometer.

The results obtained (iomeprol/iofratol 400 - 14.3 mPa·s; iomeprol 400 - 13.6 mPa·s; iofratol 400 - 30.8 mPa·s) show that the mixture viscosity is surprisingly similar to the one of the less viscous component (the monomer), taken alone, and lower than the one calculated by hypothesizing the contribution of the two components proportional to their presence in the mixture in molar fraction terms.

EXAMPLE 4

Further compositions were prepared according to the invention, by using the couple of compounds hereunder listed, in concentrations that allowed solutions at a iodine content of about 300 g (iodine)/L. The component ratio has been studied case by case to obtain a osmolal value similar to blood for each formulation.

The following mixtures have been prepared confirming the previously discussed unexpected advantages, in comparison to the solutions of each single component with the same iodine content of the mixture:

iohexol/iodixanol; iopromide/iodecol; iopromide/iotrol; iomeprol/iodecol; iomeprol/iodixanol; iopentol/iodixanol.

CLAIMS

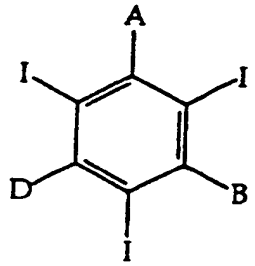
1. Aqueous injectable composition, useful to obtain images during X-ray examinations, comprising, dissolved into an aqueous medium, a mixture of:

(a) an organic compound comprising a triiodinated aromatic nucleus having, in the remaining positions, linear or branched organic residues functionally substituted,

(b) an organic compound comprising at least two triiodinated aromatic nuclei covalently bound together, in one of the non iodine substituted positions through a linear or branched and functionally substituted organic residue, being these aromatic nuclei furtherly substituted in the remaining positions by organic residues as previously defined for the compound (a),

said compounds (a) and (b) being present in the mixture in such a ratio that the iodine quantity of compound (b) can range between 10-90% in weight, preferably between 20-75%, of the total iodine amount present in the composition.

2. Composition according to claim 1, wherein compounds (a) have general formula (I)



(I)

wherein:

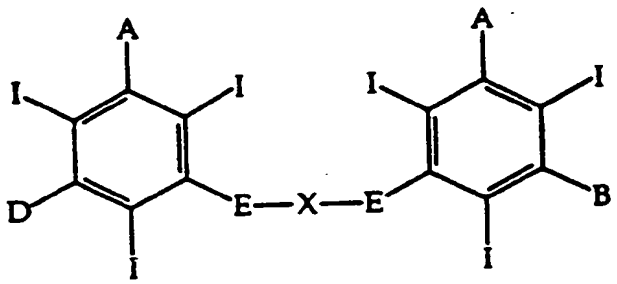
A, B, D, which are the same or different, are $-CON(R)R_1$ or $-N(R)-CO-R_2$ groups wherein

R is H or a linear or branched alkyl residue (C_1-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups,

R_1 is a linear or branched alkyl residue (C_2-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups, or by one of the two groups $-NH-CO-R_1$ or $-CO-N(R)R_1$, or R_1 is the residue of a carbohydrate, or R_1 and R, taken together, are an alkylene chain (C_3-C_7) which can be interrupted by O, S, N,

R_2 is a linear or branched alkyl residue (C_1-C_6), optionally substituted by 1-5 OH and/or alkoxy and/or hydroxyalkoxy groups, and can also include an oxo group.

3. Composition according to claim 1, wherein compounds (b) have general formula (II)



(II)

wherein:

A, B, D, which are the same or different, have the same meanings of formula I,

E, which are the same or different, are selected among $-CO-N(R)-$, $-N(R)-CO-$, $-N(COR_3)-$ groups

where R has the same meanings of formula (I) and R_3 is an alkyl residue (C_1-C_3) optionally substituted by 1-2 OH or by alkoxy or hydroxyalkoxy groups,

X is a covalent bond or a linear or branched alkylene chain (C_1-C_8), which can be substituted by 1-6 OH groups and/or -CO-NHR groups, and which can be interrupted by -O-, -S-, -N-, -N(R)-CO groups, being R as above defined in formula (I).

4. Composition according to claim 1, wherein compound (a) is selected from:
iopamidol, metrizamide, iodamide, iomeprol, iopromide, ioversol, ioglunide, iosimide, iohexol, iogulamide
and compound (b) is selected from:
iotrolan, iodixanol, iofratol, 1,3-bis-[N-(3,5-bis-(2,3-dihydroxypropyl-aminocarbonyl)-2,4,6-triiodophenyl)-N-hydroxyacetyl-amino]-propane.

5. Composition according to claims 1-4, wherein osmolality ranges between 250 and 600 mmol/kg, preferably between 280 and 400, in particular between 280 and 320 mmol/kg.

6. Composition according to claim 1, furtherly comprising additives selected from excipients, stabilisers, control agents for dissolution, anticlotting agents, water-soluble mineral salts physiologically tolerable.

7. Composition according to claim 6, wherein mineral salts are selected from halides, carbonates, bicarbonates, sulphates, phosphates of Na, K, Mg, Ca.

8. Composition according to claim 6, wherein the

anticlotting agent is selected from heparin and hirudin.

9. Composition according to claim 6, wherein excipients are selected from glycerol, polyethylenglycol, dextran.

10. Composition according to claim 6, wherein stabilisers are selected from tromethamol, EDTA, EDTA·$CaNa_2$, sodium phosphate.

11. Composition according to claim 1, wherein the total concentration of the two compounds (a) and (b) allows an iodine concentration of 200-450 g (iodine)/L or more, while osmolality is kept between 0.8-1.5 times the physiological value.

INTERNATIONAL SEARCH REPORT

Inter. ional Application No
PCT/EP 93/03613

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 050 167 (MALLINCKRODT INC) 7 January 1981 cited in the application see abstract	1,2,6,7
Y	see page 1, line 62 - page 3, line 49; claims	3,4
Y	ACTA RADIOLOGICA vol. 33 , 1992 pages 600 - 605 O. SMEDBY 'VISCOSITY OF SOME CONTEMPORARY CONTRAST MEDIA BEFORE AND AFTER MIXING WITH WHOLE BLOOD' see the whole document	3,4
A	US,A,2 613 172 (W. GALLER ET AL.) 7 October 1952 see the whole document	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the . ame patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 1994	18. 05. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Hoff, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 390 242 (NYCOMED AS) 3 October 1990 cited in the application see the whole document ---	1-11
A	WO,A,91 13636 (NYCOMED AS) 19 September 1991 see the whole document -----	1-11

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 93/03613

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3, 5-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are defined by the term "organic compound comprising...tricodinated aromatic nucleus/nuclei" and by the general formulas of claims 2-3, the search was limited to the compounds mentioned in the tables 2 and 3 and in the claim 4 (PCT:Art.6;Guidelines ..

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2050167	07-01-81	AU-A-	5856480	27-11-80
		BE-A-	883383	20-11-80
		DE-A-	3018515	04-12-80
		FR-A-	2457104	19-12-80
		JP-A-	55154920	02-12-80
		NL-A-	8002388	25-11-80
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		CN-A-	1045528	26-09-90
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		EP-A-	0463013	02-01-92
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		AU-A-	7345191	10-10-91
		CN-A-	1056058	13-11-91
		EP-A-	0521880	13-01-93
		JP-T-	5504953	29-07-93